

FIG. 1

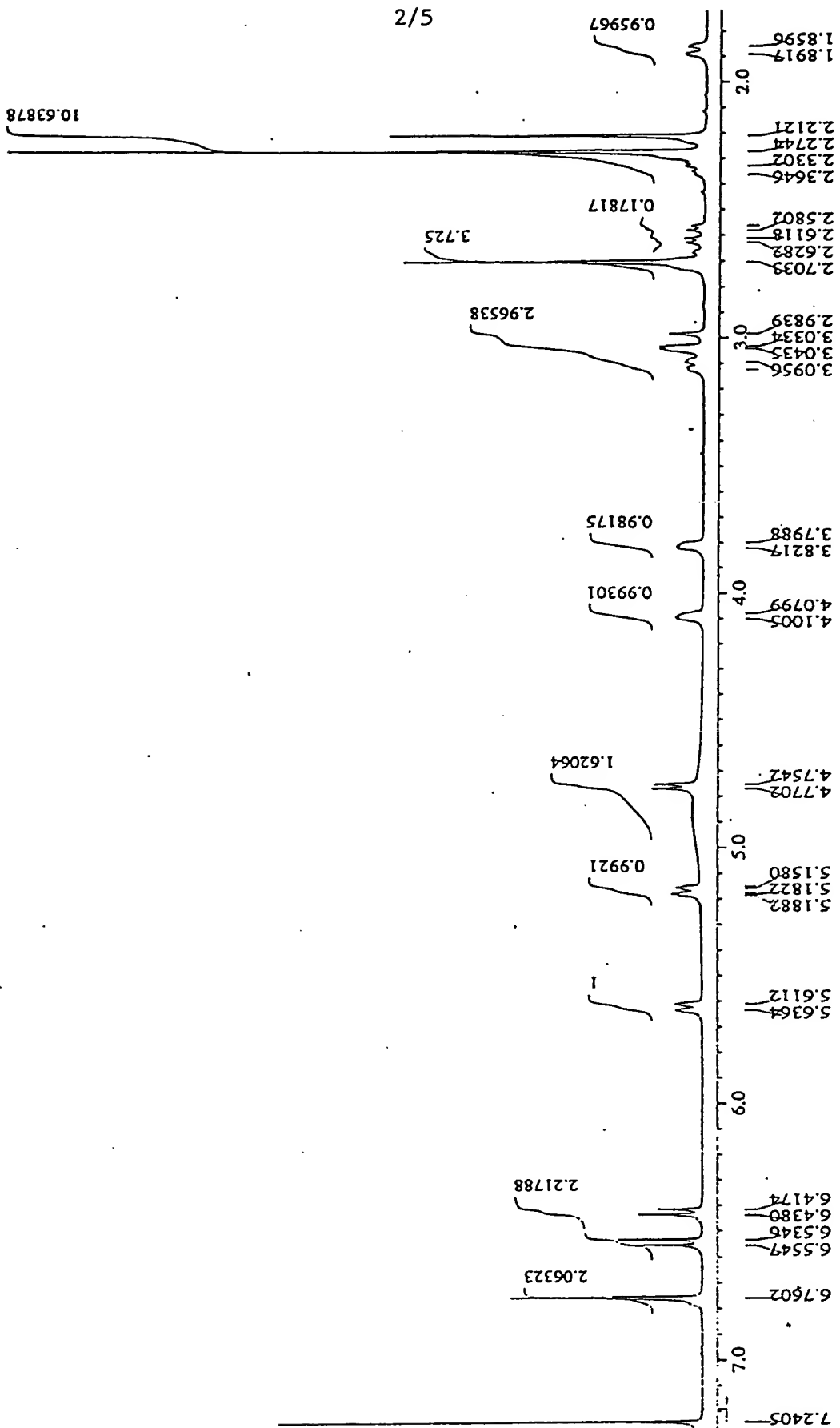


FIG. 2

[illegible]

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Chemical shift of the proton signals in the  $^1\text{H}$  spectrum  
of the morphine base and the morphine-(2,4,6)-trimethylbenzoate

Proton at the carbon No.:	Signal (Shift in ppm)	
	Morphine base	Morphinetrimethylbenzoate
15 (equatorial)	1,85	1,88
15 (axial)	2,06	2,33
10 (cis position to proton at C 9)	2,24	2,61
16 (axial)	2,41	2,70
methyl group protons at C 17	2,43	2,71
16 (equatorial)	2,59	3,11
14	2,66	3,05
10 (trans position to proton at C 9)	3,02	3,02
9	3,35	3,81
6	4,18	4,18
5	4,88	4,77
8	5,28	5,17
7	5,67	5,63
1	6,50	6,43
2	6,62	6,55
Protons of the methyl group in 4-position of the 2,4,6-trimethylbenzoic acid		2,22
Protons of the methyl groups in 2,6-position of the 2,4,6-trimethylbenzoic acid		2,28
Protons in 3,5-position at the aromatic ring of the 2,4,6-trimethylbenzoic acid		6,77

Signal at 7,25 ppm – solvent signal of the  $\text{CDCl}_3$

Signals of protons in the neighborhood of the amine function are subjected to the strongest lower field shift, due to protonation of the nitrogen, e.g.:

Proton at C 15 (axial)	+ 0,27 ppm
Proton at C 10(cis position to proton at C 9):	+ 0,37 ppm
Proton at C 16 (axial):	+ 0,29 ppm
Protons at the methyl group with C 17:	+ 0,29 ppm
Proton at C 16 (equatorial):	+ 0,52 ppm
Proton at C 9:	+ 0,46 ppm

Figur 3

Comparison skin permeation of various morphine salts

Type of skin: nude guinea pig (back); # 20/05-0455/00-95

Acceptor: 0.9% NaCl solution + 0.1% NaN<sub>3</sub>

Release temperature: 37 °C

Release vehicle: olive oil

Load donor: 2 Ma%; relative to Mph salt I

Load Mph salt/cm<sup>2</sup> skin: 787.4 µgUnit of values: µg/cm<sup>2</sup> (mean values of n=3)

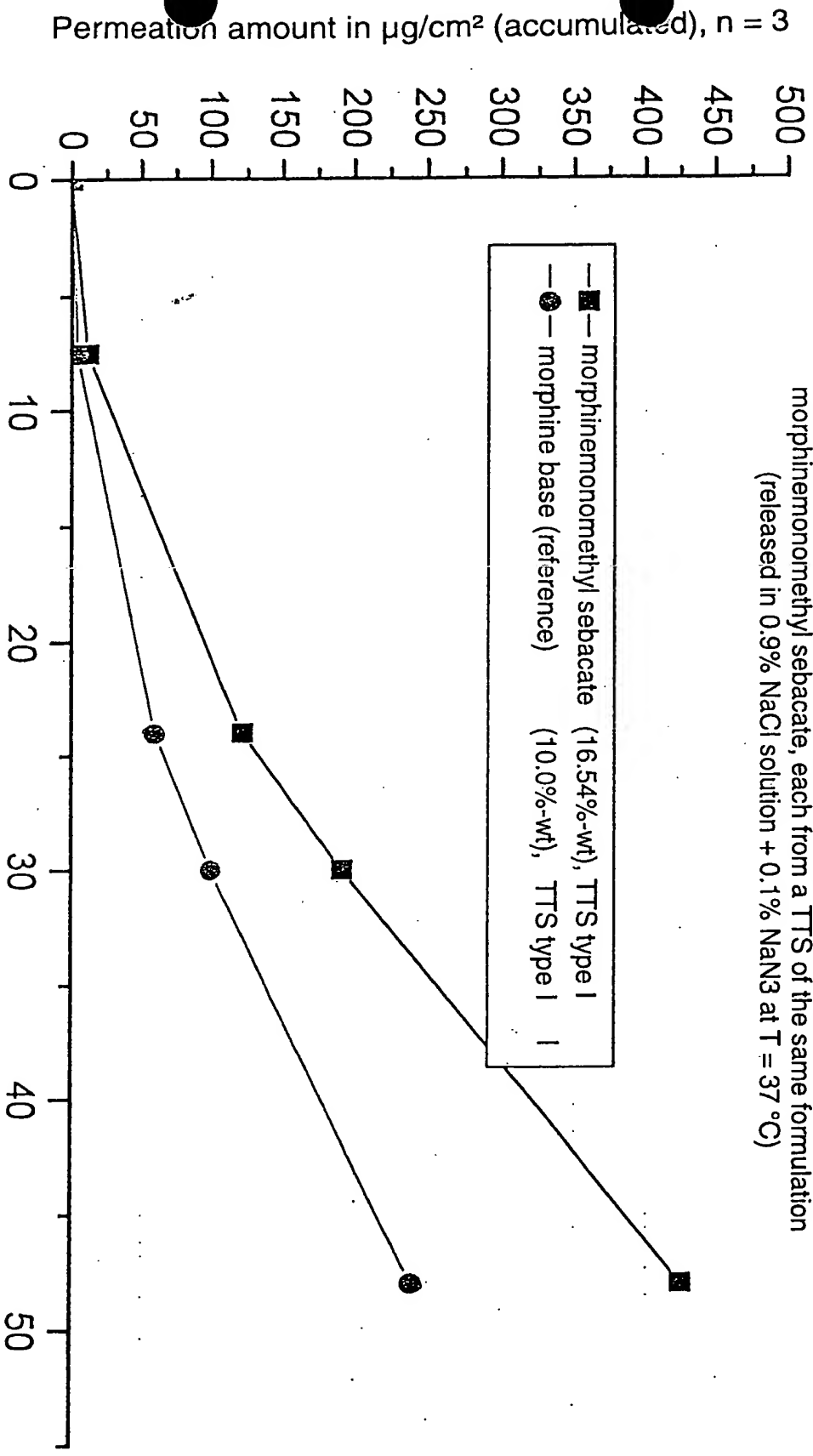
\* Flux: sum 48 h (accumulated) – sum 24 h (accumulated) / 24

Unit of values flux: µg/cm<sup>2</sup>xh

		differential permeation values					
Mph salt		7.5 h	24 h	30 h	48 h	total	flux*
Example 1	monomethyl sebacate	3,31	12,3	7,47	24,6	47,7	1,34
Example 2	p-hydroxybenzoate	24,2	172	82	196	474	11,6
Example 3	oxo-prolinate	9,82	71,2	47,4	172	301	9,16
Example 4	hexane sulfonate	2,7	18,7	14,4	63,6	99,4	3,25
Example 5	nicotinate	22,2	99,9	55,4	167	345	9,29
Example 6	p-aminobenzoate	8,56	23,6	10,5	45,6	88,3	2,34
Example 7	trimethylbenzoate	3,7	36,3	24	102	166	5,25
Example 8	liponate	1,23	12,0	8,52	19,9	41,6	1,18
Example 9	acetyl glycinate	38,1	180,0	62,4	110	390	7,17
Example 10	hippurate	22,9	83,4	41,3	109	256	6,25
Comparison Expl. 1	[base]	3,54	3,2	2,48	8,3	17,5	0,45
Comparison Expl. 2	propionate	1,55	4,74	2,66	8,54	17,5	0,47
Comparison Expl. 3	formiate	0,342	6,46	2,54	8,6	17,9	0,46

Figur 4

Figure 5



Comparison skin permeation (nude guinea pig) of morphine base and morphinemonomethyl sebacate, each from a TTS of the same formulation (released in 0.9% NaCl solution + 0.1% NaN<sub>3</sub> at T = 37 °C)

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